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=> d his

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     FILE 'CAPLUS' ENTERED AT 13:29:24 ON 02 FEB 2005
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L1             2 S STOCK/AU
L2             2 S STOCK /AU
L3          4039 S STOCK ?/AU
L4          6994 S OBESITY/TI
L5             8 S L4 AND L3
L6           470 S SIBUTRAMINE
L7             6 S L6 AND L3
               SELECT L7 RN 6

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L8             1 S E1

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L9                STRUCTURE UPLOADED
L10            4 S L9
L11           12 S L9 FUL CSS

     FILE 'CAPLUS' ENTERED AT 13:36:25 ON 02 FEB 2005
L12           76 S L11

     FILE 'REGISTRY' ENTERED AT 13:39:48 ON 02 FEB 2005

     FILE 'CAPLUS' ENTERED AT 13:41:18 ON 02 FEB 2005
L13        36425 S PAIN

=> s l12 and l13
L14            7 L12 AND L13

=> d bib abs hitstr 1-7

L14  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:72805  CAPLUS
DN   136:139829
TI   Compositions comprising sibutramine metabolites in combination with
     phosphodiesterase inhibitors
IN   Jerussi, Thomas P.; Senanayake, Chrisantha H.; Fang, Qun K.
PA   Sepracor, Inc., USA
SO   U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Ser. No. 662,135.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 5
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   US 2002010198         A1    20020124    US 2001-770663          20010129
     US 6476078            B2    20021105
     US 6331571            B1    20011218    US 1999-372158          19990811
     EP 1475086            A2    20041110    EP 2004-18454           19990823
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL
     US 6339106            B1    20020115    US 2000-662135          20000914
     WO 2002060424         A2    20020808    WO 2002-US2040          20020123
     WO 2002060424         A3    20030206
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W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2003096792	A1	20030522	US 2002-278097	20021023
	US 2003195261	A1	20031016	US 2003-395298	20030325
	US 2004067957	A1	20040408	US 2003-665448	20030922
	US 2004092481	A1	20040513	US 2003-693980	20031028
	US 2004116534	A1	20040617	US 2003-717653	20031121
	US 2004162355	A1	20040819	US 2004-769860	20040203
	US 2004180857	A1	20040916	US 2004-806415	20040323
PRAI	US 1999-372158	A2	19990811		
	US 2000-662135	A2	20000914		
	US 1998-97665P	P	19980824		
	US 1998-99306P	P	19980902		
	EP 1999-945137	A3	19990823		
	US 1999-409889	A3	19991001		
	US 2001-770663	A	20010129		
	US 2001-806	A3	20011204		
	US 2002-160033	A3	20020604		
	US 2002-278097	A3	20021023		

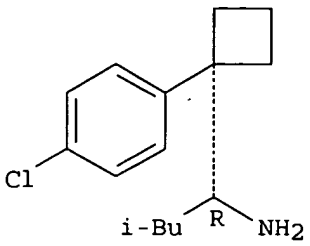
AB Methods are disclosed for the treatment and prevention of disorders and conditions such as, but are not limited to: eating disorders; weight gain; obesity; irritable bowel syndrome; obsessive-compulsive disorders; platelet adhesion; apnea; affective disorders such as attention deficit disorders, depression, and anxiety; male and female sexual function disorders; restless leg syndrome; osteoarthritis; substance abuse including nicotine and cocaine addiction; narcolepsy; **pain** such as neuropathic **pain**, diabetic neuropathy, and chronic **pain**; migraines; cerebral function disorders; chronic disorders such as premenstrual syndrome; and incontinence. Pharmaceutical compns. and dosage forms are also disclosed which comprise a racemic or optically pure sibutramine metabolite and an optional drug. Sibutramine free base was prepared by the reaction of chlorbenzylnitrile dibromopropane in the presence of NaH in DMSO, followed by the treatment of the resulting 1-(4-chlorophenyl)cyclobutanecarbonitrile with isobutylmagnesium bromide and finally treatment with HCHO. The fee base was resolved into the (R) and (S) isomers and converted into their metabolites. Hard gelatin capsules contained racemic or optically pure sibutramine metabolite 5.0, microcryst. cellulose 90.0, pregelatinized starch 100.3, croscarmellose sodium 7.0, and Mg stearate 0.2 mg.

IT **229639-56-9P 229639-57-0P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

RN 229639-56-9 CAPLUS

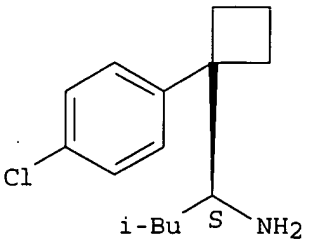
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

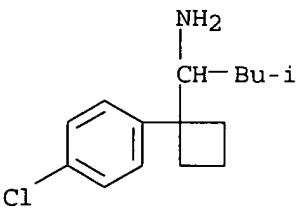


RN 229639-57-0 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



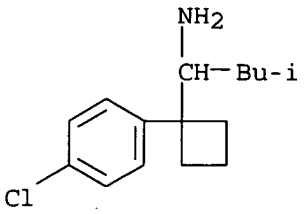
IT **84467-54-9P 259729-92-5P 259729-95-8P**
389056-70-6P 389056-73-9P 389056-74-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
RN 84467-54-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



RN 259729-92-5 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

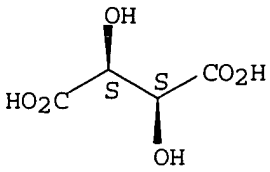
CRN 84467-54-9
CMF C15 H22 Cl N



CM 2

CRN 147-71-7
CMF C4 H6 O6

Absolute stereochemistry.

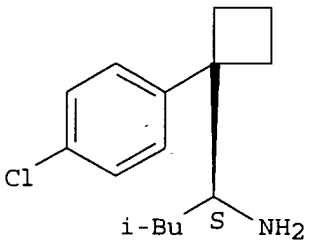


RN 259729-95-8 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-57-0
CMF C15 H22 Cl N

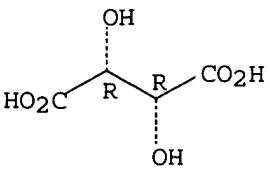
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

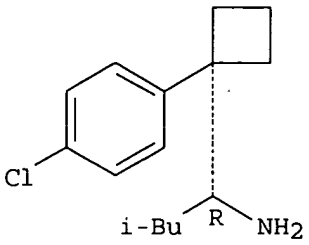


RN 389056-70-6 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-56-9
CMF C15 H22 Cl N

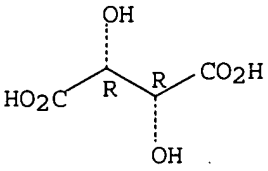
Absolute stereochemistry. Rotation (+).



CM 2

CRN 87-69-4
CMF C4 H6 O6

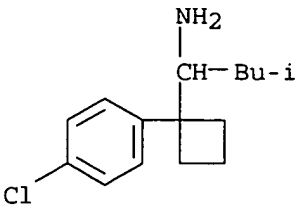
Absolute stereochemistry.



RN 389056-73-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

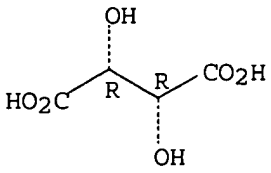
CRN 84467-54-9
CMF C15 H22 Cl N



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.

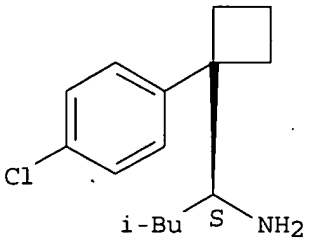


RN 389056-74-0 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)-, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-57-0
CMF C15 H22 Cl N

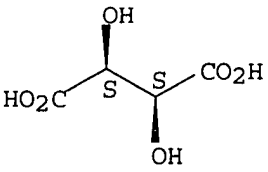
Absolute stereochemistry. Rotation (-).



CM 2

CRN 147-71-7
CMF C4 H6 O6

Absolute stereochemistry.



L14 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:51989 CAPLUS
DN 136:96083
TI Methods of using and compositions comprising (+)-sibutramine optionally in combination with other pharmacologically active compounds
IN Young, James W.; Jerussi, Thomas P.
PA USA
SO U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U. S. Ser. No. 442,263.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

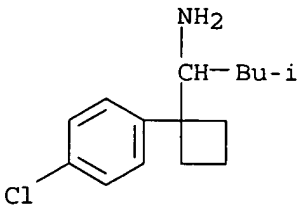
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002006964	A1	20020117	US 2001-770393	20010129
	WO 2002060427	A2	20020808	WO 2002-US2038	20020123
	WO 2002060427	A3	20030213		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003078303	A1	20030424	US 2002-295871	20021118
PRAI	US 1995-442263	A2	19950516		
	US 2001-770393	A	20010129		

AB This invention encompasses methods for the treatment and prevention of disorders that include, but are not limited to, eating disorders; weight gain; obesity; irritable bowel syndrome; obsessive-compulsive disorders; platelet adhesion; apnea; affective disorders such as attention deficit disorders, depression, and anxiety; male and female sexual function disorders; restless leg syndrome; osteoarthritis; substance abuse including nicotine and cocaine addiction; narcolepsy; **pain** such as neuropathic **pain**, diabetic neuropathy, and chronic **pain**; migraines; cerebral function disorders; chronic disorders such as premenstrual syndrome; and incontinence. The invention further encompasses pharmaceutical compns. and dosage forms which comprise optically pure (+)-sibutramine, optionally in combination with a phosphodiesterase inhibitor or a lipase inhibitor.

IT **84467-54-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

RN 84467-54-9 CAPLUS

CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:51988 CAPLUS
DN 136:107551
TI Method of using and compositions comprising (-) sibutramine optionally in combination with other pharmacologically active compounds
IN Young, James W.; Jerussi, Thomas P.
PA USA
SO U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 721,669.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 2002006963	A1	20020117	US 2001-770665	20010129
	WO 2002060428	A2	20020808	WO 2002-US2039	20020123
	WO 2002060428	A3	20021219		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 1992-903040	B1	19920623
	US 1995-461608	B1	19950605
	US 2000-721669	A2	20001127
	US 2001-770665	A	20010129

AB This invention encompasses methods for the treatment and prevention of disorders that include, but are not limited to, eating disorders; weight gain; obesity; irritable bowel syndrome; obsessive-compulsive disorders; platelet adhesion; apnea; affective disorders such as attention deficit disorders, depression, and anxiety; male and female sexual function disorders; restless leg syndrome; osteoarthritis; substance abuse including nicotine and cocaine addiction; narcolepsy; **pain** such as neuropathic **pain**, diabetic neuropathy, and chronic **pain**; migraines; cerebral function disorders; chronic disorders such as premenstrual syndrome; and incontinence. The invention further encompasses pharmaceutical compns. and dosage forms which comprise optically pure (-) sibutramine, optionally in combination with a phosphodiesterase inhibitor or a lipase inhibitor. A solution of 21.7 g L-dibenzyltartaric acid ("L-DBTA") in Et acetate was added to a solution of 12.3 g racemic sibutramine in Et acetate and the reaction mixture was heated to reflux and cooled to room temperature The white precipitate was collected and the solid was then suspended in Et acetate and heated at reflux for 30 min. The solid was collected and further crystallized in iso-Pr alc. to give 11.3 g of (-)-sibutramine L-DBTA (yield 76%). Free base was obtained by treatment of (-)-sibutramine L-DBTA with saturated aqueous NaHCO3 and extracted with chloroform. A pharmacol. study was conducted to determine the relative potency, comparative efficacy, binding affinity, and toxicity of the enantiomers and racemic mixture of sibutramine. A capsule contained (-) sibutramine 10.0, lactose 70.0, corn starch 19.5, and magnesium stearate 0.05 mg.

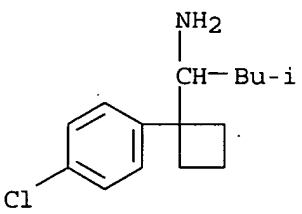
IT **84467-54-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(method of using and compns. comprising (-) sibutramine optionally in combination with other pharmacol. active compds.)

RN 84467-54-9 CAPLUS

CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



L14 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:526047 CAPLUS
DN 135:122299
TI Synthesis of racemic and optically pure desmethylsibutramine, didesmethylsibutramine, oral formulations comprised thereof and their use as dopamine reuptake inhibitors
IN Senanayake, Chrisantha H.; Fang, Qun K.; Han, Zhengxu; Krishnamurthy, Dhileepkumar
PA Sepracor Inc., USA
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001051453	A1	20010719	WO 2001-US762	20010110
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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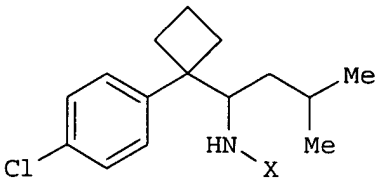
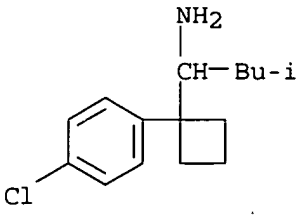
OS MARPAT 135:122299
GI



I

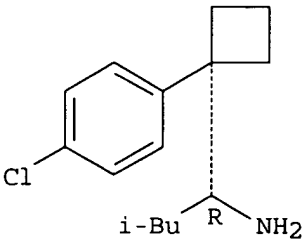
AB Racemic and optically pure sibutramine metabolites, desmethyl- (I, X = Me) and didesmethylsibutramine I (X = H; II) were prepared Addition of i-butylmagnesium bromide to 1-(4-chlorophenyl)cyclobutanecarbonitrile followed by MeOH quench and treatment with NaBH4 produced II. II was converted to the N-formyl derivative and reduced to give I. Resolution with (R)-mandelic acid furnished (R)-I. Sibutramine isomers are inhibitors of norepinephrine (NE) and 5-HT uptake and bind to muscarinic receptors while metabolites I and II were found to have affinity for NE, 5-HT and negligible activity at muscarinic sites. At NE reuptake sites, (+)-I had IC50 = 4 nM (vs. (-)-I IC50 = 870 nM), and reuptake site binding selectivity for NE/5-HT = 12. A lactose free solid oral dosage hard gelatin capsule and tablet formulation was provided. Methods to treat neuropathic **pain** and diabetic peripheral neuropathy were claimed.

IT **84467-54-9P 229639-56-9P 229639-57-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of racemic and optically pure desmethylsibutramine, didesmethylsibutramine, oral formulations comprised thereof and their use as dopamine reuptake inhibitors)
RN 84467-54-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



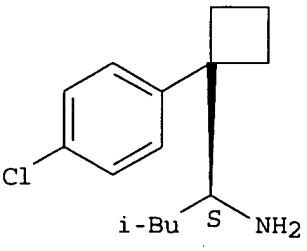
RN 229639-56-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 229639-57-0 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

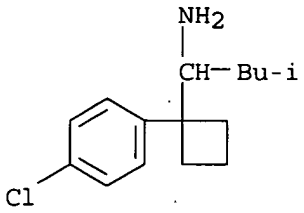


IT **259729-92-5P 259729-93-6P 259729-95-8P**
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of racemic and optically pure desmethylsibutramine, didesmethylsibutramine, oral formulations comprised thereof and their use as dopamine reuptake inhibitors)
RN 259729-92-5 CAPLUS

CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

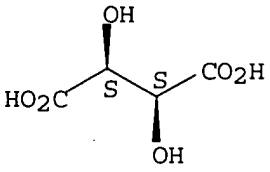
CRN 84467-54-9
CMF C15 H22 Cl N



CM 2

CRN 147-71-7
CMF C4 H6 O6

Absolute stereochemistry.

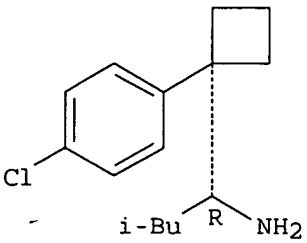


RN 259729-93-6 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)-, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-56-9
CMF C15 H22 Cl N

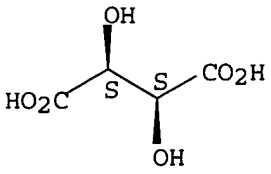
Absolute stereochemistry. Rotation (+).



CM 2

CRN 147-71-7
CMF C4 H6 O6

Absolute stereochemistry.

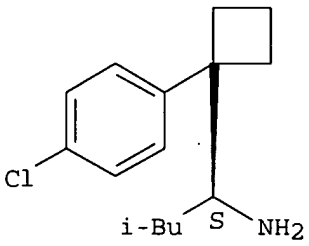


RN 259729-95-8 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-57-0
CMF C15 H22 Cl N

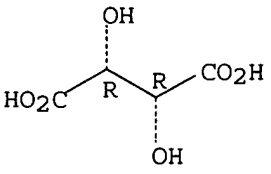
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

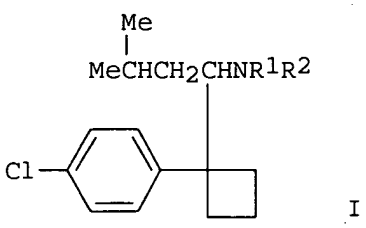
L14 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:688075 CAPLUS
DN 133:232864
TI Treatment of neuropathic **pain** or fibromyalgia with sibutramine and N-demethyl derivatives thereof
IN Mendel, Carl M.; Seaton, Timothy B.; Weinstein, Steve P.
PA Knoll Pharmaceutical Company, USA
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000056318	A1	20000928	WO 2000-US7204	20000317
	W: AT, AU, BG, BR, CA, CN, CZ, DE, DK, ES, FI, GB, HR, HU, ID, IL, IN, IS, JP, KR, LT, LU, LV, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TR, UA, ZA				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6803387	B1	20041012	US 2000-528798	20000317
	US 2004198837	A1	20041007	US 2004-828607	20040421
PRAI	US 1999-125113P	P	19990319		
	US 2000-528798	A1	20000317		

OS MARPAT 133:232864

GI

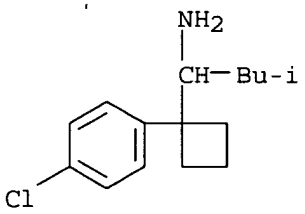


AB Compds. I (R1, R2 = H, Me) or a pharmaceutically acceptable salt thereof (e.g. N,N,-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine-HCl, optionally in the form of its monohydrate) are used for treating fibromyalgia or neuropathic **pain**, e.g. **pain** associated with diabetes mellitus, shingles, nerve injury and varied peripheral neuropathies.

IT **84467-54-9 84467-54-9D**, enantiomers **229639-56-9 229639-57-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sibutramine and N-demethyl derivs. for treatment of neuropathic **pain** and fibromyalgia)

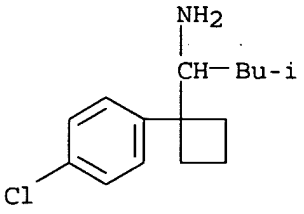
RN 84467-54-9 CAPLUS

CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



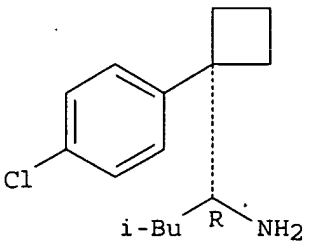
RN 84467-54-9 CAPLUS

CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



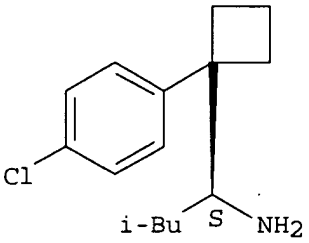
RN 229639-56-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 229639-57-0 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

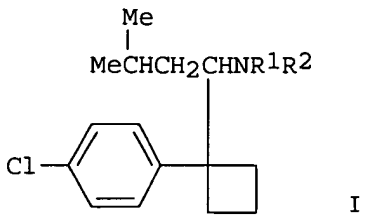
L14 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:688072 CAPLUS
DN 133:232862
TI Treatment of **pain** with sibutramine and N-demethyl derivatives thereof
IN Mendel, Carl M.; Seaton, Timothy B.; Weinstein, Steve P.
PA Knoll Pharmaceutical Company, USA
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000056315	A1	20000928	WO 2000-US7178	20000317
	W: AT, AU, BG, BR, CA, CN, CZ, DE, DK, ES, FI, GB, HR, HU, ID, IL, IN, IS, JP, KR, LT, LU, LV, MX, NO, NZ, PL, PT, RO, RU, SE, SG,				

SI, SK, TR, UA, ZA
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

	US 6376553	B1	20020423	US 2000-528036	20000317
PRAI	US 1999-125120P	P	19990319		

OS MARPAT 133:232862
GI

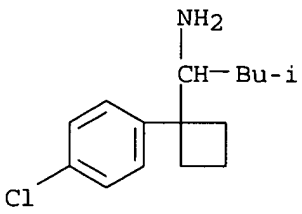


I

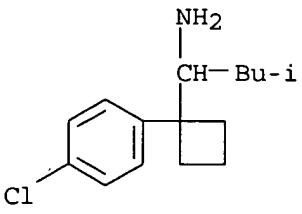
AB Compds. I (R1, R2 = H, Me) or a pharmaceutically acceptable salt thereof (e.g. N,N,-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine-HCl, optionally in the form of its monohydrate) are used for treating **pain**, e.g. low back **pain**.

IT **84467-54-9 84467-54-9D**, enantiomers **229639-56-9 229639-57-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sibutramine and N-demethyl derivs. for treatment of **pain**)

RN 84467-54-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)

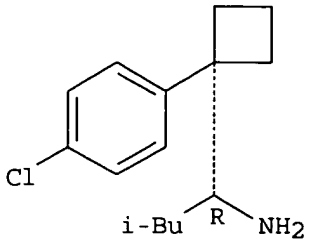


RN 84467-54-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



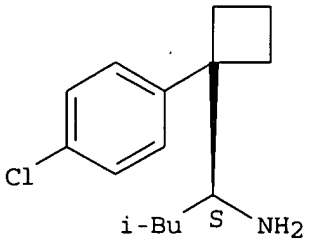
RN 229639-56-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 229639-57-0 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:144721 CAPLUS
DN 132:189679
TI Methods of using and compositions comprising dopamine reuptake inhibitors
IN Jerussi, Thomas P.; Senanayake, Chrisantha H.; Fang, Qun K.
PA Sepracor Inc., USA
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000010551	A2	20000302	WO 1999-US19167	19990823
	WO 2000010551	A3	20000921		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6331571	B1	20011218	US 1999-372158	19990811
	CA 2341441	AA	20000302	CA 1999-2341441	19990823
	AU 9957817	A1	20000314	AU 1999-57817	19990823
	AU 772303	B2	20040422		
	EP 1107746	A2	20010620	EP 1999-945137	19990823
	EP 1107746	B1	20041013		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO

BR 9913325	A	20011002	BR 1999-13325	19990823
JP 2002523366	T2	20020730	JP 2000-565873	19990823
NZ 510193	A	20030926	NZ 1999-510193	19990823
AT 279184	E	20041015	AT 1999-945137	19990823
RU 2238084	C2	20041020	RU 2001-107831	19990823
EP 1475086	A2	20041110	EP 2004-18454	19990823

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

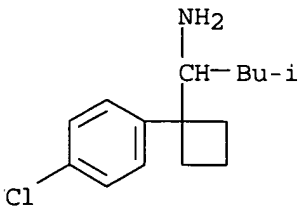
ZA 2001001498	A	20020222	ZA 2001-1498	20010222
NO 2001000943	A	20010423	NO 2001-943	20010223
US 2002188029	A1	20021212	US 2001-806	20011204
US 6538034	B2	20030325		
US 2003195261	A1	20031016	US 2003-395298	20030325
US 2004180857	A1	20040916	US 2004-806415	20040323
PRAI US 1998-97665P	P	19980824		
US 1998-99306P	P	19980902		
US 1999-372158	A	19990811		
EP 1999-945137	A3	19990823		
WO 1999-US19167	W	19990823		
US 1999-409889	A3	19991001		
US 2001-806	A3	20011204		
US 2002-160033	A3	20020604		

AB Methods are disclosed for the treatment and prevention of disorders and conditions including, but are not limited to, erectile dysfunction, affective disorders, weight gain, cerebral functional disorders, **pain**, obsessive-compulsive disorder, substance abuse, chronic disorders, anxiety, eating disorders, migraines, and incontinence. The methods comprise the administration of a dopamine reuptake inhibitor and optionally an addnl. pharmacol. active compound Pharmaceutical compns. and dosage forms are also disclosed that comprise a dopamine reuptake inhibitor and optionally an addnl. pharmacol. active compound Preferred dopamine reuptake inhibitors are racemic or optically pure sibutramine metabolites and pharmaceutically acceptable salts, solvates, and clathrates thereof. Preferred addnl. pharmacol. active compds. include drugs that affect the central nervous system, such as 5-HT3, antagonists.

IT **84467-54-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(dopamine reuptake inhibitors, pharmaceutical compns., and therapeutic use, including with other agents)

RN 84467-54-9 CAPLUS

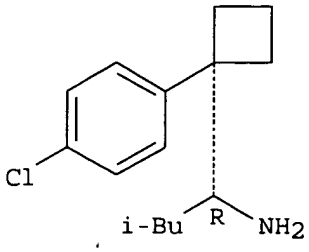
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)- (9CI) (CA INDEX NAME)



IT **229639-56-9 229639-57-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dopamine reuptake inhibitors, pharmaceutical compns., and therapeutic use, including with other agents)

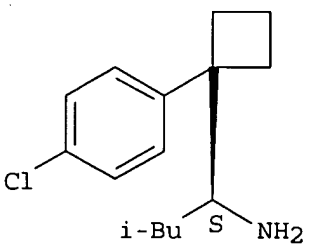
RN 229639-56-9 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 229639-57-0 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

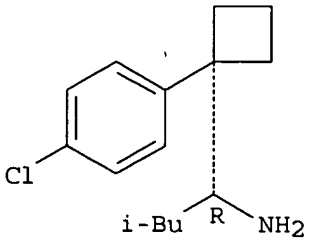


IT **259729-93-6P 259729-95-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(dopamine reuptake inhibitors, pharmaceutical compns., and therapeutic use, including with other agents)
RN 259729-93-6 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αR)-, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-56-9
CMF C15 H22 Cl N

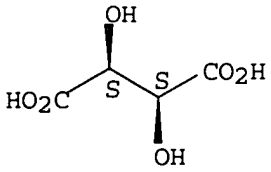
Absolute stereochemistry. Rotation (+).



CM 2

CRN 147-71-7
CMF C4 H6 O6

Absolute stereochemistry.

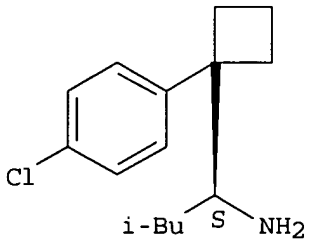


RN 259729-95-8 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (αS)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 229639-57-0
CMF C15 H22 Cl N

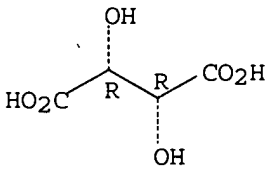
Absolute stereochemistry. Rotation (-).



CM 2

CRN 87-69-4
CMF C4 H6 O6

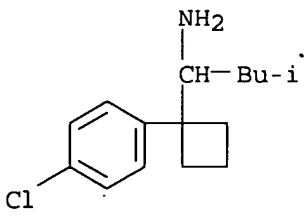
Absolute stereochemistry.



IT **259729-92-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; dopamine reuptake inhibitors, pharmaceutical compns., and therapeutic use, including with other agents)
RN 259729-92-5 CAPLUS
CN Cyclobutanemethanamine, 1-(4-chlorophenyl)-α-(2-methylpropyl)-, (2S,3S)-2,3-dihydroxybutanedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

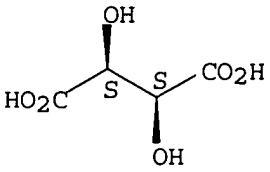
CRN 84467-54-9
CMF C15 H22 Cl N



CM 2

CRN 147-71-7
CMF C4 H6 O6

Absolute stereochemistry.



=> d his

(FILE 'HOME' ENTERED AT 13:27:59 ON 02 FEB 2005)

FILE 'REGISTRY' ENTERED AT 13:28:05 ON 02 FEB 2005
E DIDESMETHYLSIBUTRA/CN

FILE 'CAPLUS' ENTERED AT 13:29:24 ON 02 FEB 2005
E STOCK/AU
L1 2 S STOCK/AU
L2 2 S STOCK /AU
L3 4039 S STOCK ?/AU
L4 6994 S OBESITY/TI
L5 8 S L4 AND L3
L6 470 S SIBUTRAMINE
L7 6 S L6 AND L3
SELECT L7 RN 6

FILE 'REGISTRY' ENTERED AT 13:32:15 ON 02 FEB 2005
L8 1 S E1

FILE 'REGISTRY' ENTERED AT 13:35:34 ON 02 FEB 2005
L9 STRUCTURE UPLOADED
L10 4 S L9
L11 12 S L9 FUL CSS

FILE 'CAPLUS' ENTERED AT 13:36:25 ON 02 FEB 2005
L12 76 S L11

FILE 'REGISTRY' ENTERED AT 13:39:48 ON 02 FEB 2005

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     FILE 'CAPLUS' ENTERED AT 13:41:18 ON 02 FEB 2005
L13         36425 S PAIN
L14             7 S L12 AND L13

=> s l13 and l12
L15             7 L13 AND L12

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      38.27     322.54

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -5.11     -17.65

FILE 'MEDLINE' ENTERED AT 13:43:24 ON 02 FEB 2005

 FILE LAST UPDATED: 29 JAN 2005 (20050129/UP).  FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 Warning: The search L-number/HUMAN limit is missing from records indexed
 with the new 2005 MeSH (records added since December 19, 2004).  Until
 this is corrected, include HUMANS/CT and 20041219-20051231/ED in
 searches to limit results to humans for this time period.

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l15
        242065 PAIN
             6 L11
L16          0 L13 AND L12

=> d his

     (FILE 'HOME' ENTERED AT 13:27:59 ON 02 FEB 2005)

     FILE 'REGISTRY' ENTERED AT 13:28:05 ON 02 FEB 2005
               E DIDESMETHYLSIBUTRA/CN

     FILE 'CAPLUS' ENTERED AT 13:29:24 ON 02 FEB 2005
               E STOCK/AU
L1             2 S STOCK/AU
L2             2 S STOCK /AU
L3          4039 S STOCK ?/AU
L4          6994 S OBESITY/TI
L5             8 S L4 AND L3
L6           470 S SIBUTRAMINE
L7             6 S L6 AND L3
               SELECT L7 RN 6

     FILE 'REGISTRY' ENTERED AT 13:32:15 ON 02 FEB 2005
L8             1 S E1
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     FILE 'REGISTRY' ENTERED AT 13:35:34 ON 02 FEB 2005
L9                STRUCTURE UPLOADED
L10            4 S L9
L11           12 S L9 FUL CSS

     FILE 'CAPLUS' ENTERED AT 13:36:25 ON 02 FEB 2005
L12           76 S L11

     FILE 'REGISTRY' ENTERED AT 13:39:48 ON 02 FEB 2005

     FILE 'CAPLUS' ENTERED AT 13:41:18 ON 02 FEB 2005
L13        36425 S PAIN
L14            7 S L12 AND L13
L15            7 S L13 AND L12

     FILE 'MEDLINE' ENTERED AT 13:43:24 ON 02 FEB 2005
L16            0 S L15

=> s l11
L17            6 L11

=> d bib abs hitstr 1-6
'HITSTR' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, CM, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRI ---- TI, CM, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, CM, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and
PY.

To display a particular field or fields,  enter the display field
codes.  For a list of display field codes, enter 'HELP DFIELDS'
at an arrow prompt (=>).  Examples of formats include: 'BIB';
'AB'; 'SO,ST'.  You may specify the format fields in any order,
and the information will be displayed in the same order as the
format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be
used with the DISPLAY ACC command to display the record for a
specified Accession Number.
ENTER DISPLAY FORMAT (BIB):bib abs

L17  ANSWER 1 OF 6     MEDLINE on STN
AN   2004102626     MEDLINE
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DN PubMed ID: 14992000
TI Pharmacokinetics of sibutramine hydrochloride in Chinese healthy volunteers.
AU Chen Jun; Lu Wei; Jiang Xin-guo; Rong Zheng-xing; Huang Xia; Chen Hong-zhuan
CS Department of Pharmaceutics, School of Pharmacy, Fudan University, Shanghai 200032, China.
SO Yao xue xue bao = Acta pharmaceutica Sinica, (2003 Nov) 38 (11) 850-3.
Journal code: 21710340R. ISSN: 0513-4870.
CY China
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200409
ED Entered STN: 20040303
Last Updated on STN: 20040909
Entered Medline: 20040908
AB AIM: To evaluate the pharmacokinetic profiles of the pharmacologically active primary amine metabolite of sibutramine, N-di-desmethyl sibutramine (BTS 54505) in Chinese origin. METHODS: According to a randomized cross-over design, a single oral dose of 20 mg of sibutramine hydrochloride capsule was given to 20 healthy Chinese young volunteers. After dosing, serial blood samples were collected for a period of 72 h. BTS 54505 concentration in plasma was analyzed by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry. RESULTS: Various pharmacokinetic parameters including AUC0-t, AUC0-infinity, Cmax, Tmax, T1/2, Kelm and MRT were determined for both test and reference capsules and found to be in good agreement with literature values. CONCLUSION: The test and reference sibutramine capsules were bioequivalent.

L17 ANSWER 2 OF 6 MEDLINE on STN
AN 2004095770 MEDLINE
DN PubMed ID: 14634034
TI Acute cardiovascular effects of sibutramine in conscious rats.
AU Woolard Jeanette; Bennett Terence; Dunn William R; Heal David J; Aspley Susan; Gardiner Sheila M
CS School of Biomedical Sciences, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, UK.
SO Journal of pharmacology and experimental therapeutics, (2004 Mar) 308 (3) 1102-10.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200404
ED Entered STN: 20040302
Last Updated on STN: 20040407
Entered Medline: 20040406
AB Sibutramine is a serotonin and norepinephrine reuptake inhibitor, used in the treatment of obesity. In this study, cardiovascular effects of sibutramine (0.9, 3, or 9 mg kg(-1) i.p.) were measured in conscious Sprague-Dawley rats, in the absence and presence of beta- and/or alpha-adrenoceptor antagonism (with propranolol and/or phentolamine, respectively). Sibutramine caused pressor and tachycardic effects, with celiac and mesenteric vasoconstrictions, and hyperemic hindquarters vasodilatation. Pretreatment with propranolol inhibited the tachycardic and hindquarters vasodilator effect of sibutramine, whereas phentolamine inhibited the pressor and vasoconstrictor effects of sibutramine. In the presence of phentolamine, sibutramine caused hyperemic mesenteric

vasodilatation. In preconstricted, isolated, mesenteric vessels, sibutramine and its metabolites BTS 54505 (N-desmethylsibutramine) and BTS 54354 (N-didesmethylsibutramine) (10 microM) produced significant vasodilations. Neither sibutramine nor BTS 54505 enhanced vessel sensitivity to norepinephrine, whereas BTS 54 354 produced a significant leftward shift in the concentration-response curve to norepinephrine. Collectively, the results indicate that the overt cardiovascular effects of sibutramine involve alpha-adrenoceptor-mediated celiac and mesenteric vasoconstrictions, and beta-adrenoceptor-mediated hindquarters vasodilatation and tachycardia. The mesenteric vasodilator response to sibutramine, seen in the presence of phentolamine, may be a direct effect of the drug and/or its metabolites, on vessel tone. The cardiovascular effects of sibutramine in vivo may be secondary to inhibition of peripheral and/or central reuptake of monoamines by the metabolites BTS 54354 and/or BTS 54505. It remains to explain why BTS 54354, but not BTS 54505, enhanced norepinephrine sensitivity in vitro, because both metabolites are potent inhibitors of the norepinephrine transporter.

L17 ANSWER 3 OF 6 MEDLINE on STN
AN 2002430309 MEDLINE
DN PubMed ID: 12187403
TI Mechanism of the thermogenic effect of Metabolite 2 (BTS 54 505), a major pharmacologically active metabolite of the novel anti-obesity drug, sibutramine.
AU Liu Y-L; Heal D J; Stock M J
CS Department of Physiology, St George's Hospital Medical School, University of London, UK.. yliu@sghms.ac.uk
SO International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity, (2002 Sep) 26 (9) 1245-53.
Journal code: 9313169. ISSN: 0307-0565.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20020821
Last Updated on STN: 20030306
Entered Medline: 20030305
AB OBJECTIVE: To investigate the pharmacological mechanisms underlying the induction of thermogenesis by Metabolite 2 (M2; BTS 54 505), a major pharmacologically active metabolite of the anti-obesity drug, sibutramine. DESIGN: Adult female Wistar rats were treated with M2 or vehicle, with or without various monoamine receptor antagonists, prazosin, RS79948, metergoline, propranolol and (+)butaclamol. MEASUREMENTS: Colonic temperature and food intake at room temperature (21+/-1 degrees C), thermoregulatory behavioural response, operant responding for exogenous heat at -8 degrees C and oxygen consumption at thermoneutrality (29 degrees C). RESULTS: M2 (10 mg/kg, p.o.) significantly increased colonic temperature during the 4.5 h period following drug administration. This effect was abolished by the non-selective 5-HT receptor antagonist, metergoline (1 mg/kg, p.o.), and alpha(1)-adrenoceptor antagonist, prazosin (1 mg/kg, p.o.), measured at 1.5-2.5 h post-M2 administration, and was partially antagonized by each antagonist at 3.5-4.5 h. The non-selective beta-adrenoceptor antagonist, propranolol (1 mg/kg, p.o.), had no effect on the M2-induced increase in colonic temperature, whereas at 20 mg/kg (p.o.), propranolol partially inhibited the effect of M2 on colonic temperature. By contrast, the selective alpha(2)-adrenoceptor antagonist, RS79948 (1 mg/kg, p.o.), and the D2/D1 receptor antagonist, (+)butaclamol (200 micro g/kg, p.o.), did not alter the effect of M2 on colonic temperature. In the thermoregulatory study, M2 (10 mg/kg, i.p.)-treated rats required significantly less radiant heat at -8 degrees C to maintain body temperature, and this effect was not affected by the

D2/D1 receptor antagonist (+)butaclamol (100 micro g/kg(-1), i.p.). The hypophagia induced by M2 (10 mg/kg) measured up to 24 h was partially antagonized by the alpha(1)-adrenoceptor antagonist, prazosin, whereas metergoline, RS79948, propranolol and (+)butaclamol had no effect on M2-induced hypophagia. CONCLUSION: It is concluded that 5-HT, alpha(1)- and beta(3)-adrenoceptors are involved in the induction of thermogenesis by M2, whereas the hypophagic effect is mainly mediated via alpha(1)-adrenoceptors. These findings are consistent with M2 increasing 5-HT and noradrenaline tone via potent reuptake inhibition which subsequently results in increased efferent sympathetic activity to brown adipose tissue (BAT).

L17 ANSWER 4 OF 6 MEDLINE on STN
AN 1999000468 MEDLINE
DN PubMed ID: 9786502
TI A comparison of the effects on central 5-HT function of sibutramine hydrochloride and other weight-modifying agents.
AU Heal D J; Cheetham S C; Prow M R; Martin K F; Buckett W R
CS Knoll Pharmaceuticals Research & Development, Nottingham.
SO British journal of pharmacology, (1998 Sep) 125 (2) 301-8.
Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199901
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19990104
AB 1. Effects on 5-HT function of sibutramine and its active metabolites, BTS 54 354 and BTS 54 505, were compared with fluoxetine, (+)-fenfluramine and (+)-amphetamine. 2. In vitro sibutramine weakly inhibited [3H]-5-HT uptake into brain synaptosomes. BTS 54 354, BTS 54 505 and fluoxetine were powerful [3H]-5-HT uptake inhibitors, whereas (+)-fenfluramine and (+)-amphetamine were very much weaker. Conversely, whilst sibutramine, its metabolites and fluoxetine did not release [3H]-5-HT from brain slices at < or = 10(-5)M, (+)-fenfluramine and (+)-amphetamine concentration-dependently increased [3H]-5-HT release. 3. Sibutramine and fluoxetine had no effect on 5-hydroxytryptophan (5-HTP) accumulation in either frontal cortex or hypothalamus at doses < 10 mg kg(-1). In contrast, (+)-amphetamine (> or = 3 mg kg(-1)) reduced 5-HTP in hypothalamus, whilst (+)-fenfluramine (> or =1 mg kg(-1)) decreased 5-HTP in both regions. 4. Sibutramine (10 mg kg(-1) i.p.) and fluoxetine (10 mg kg(-1) i.p.) produced slow, prolonged increases of extracellular 5-HT in the anterior hypothalamus. In contrast, (+)-fenfluramine (3 mg kg(-1) i.p.) and (+)-amphetamine (4 mg kg(-1) i.p.) induced rapid, short-lasting increases in extracellular 5-HT. 5. Only (+)-fenfluramine (10 mg kg(-1)) altered 5-HT2A receptors in rat frontal cortex when given for 14 days, producing a 61% reduction in receptor number and a 18% decrease in radioligand affinity. 6. These results show that sibutramine powerfully enhances central 5-HT function via its secondary and primary amine metabolites; this effect, like that of fluoxetine, is almost certainly mediated through 5-HT uptake inhibition. By contrast, (+)-fenfluramine enhances 5-HT function predominantly by increasing 5-HT release. (+)-Amphetamine, though weaker than (+)-fenfluramine, also enhances 5-HT function by release.

L17 ANSWER 5 OF 6 MEDLINE on STN
AN 1998019284 MEDLINE
DN PubMed ID: 9353373
TI In vivo criteria to differentiate monoamine reuptake inhibitors from releasing agents: sibutramine is a reuptake inhibitor.
AU Gundlah C; Martin K F; Heal D J; Auerbach S B

CS Department of Biological Sciences, Rutgers University, Piscataway, New Jersey 08855, USA.
NC MH51080A (NIMH)
SO Journal of pharmacology and experimental therapeutics, (1997 Nov) 283 (2) 581-91.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971208
AB Because monoamine reuptake inhibitors and releasing agents both increase extracellular neurotransmitter levels, establishing in vivo experimental criteria for their classification has been difficult. Using microdialysis in the hypothalamus of unanesthetized rats, we provide evidence that serotonin- (5-HT) selective and nonselective reuptake inhibitors can be distinguished from the 5-HT-releasing agent fenfluramine by four criteria: 1) Systemic fenfluramine produces a much greater increase in 5-HT than the reuptake inhibitors. 2) The 5-HT somatodendritic autoreceptor agonist, (+/-)-8-hydroxy-(dipropylamino)tetralin (8-OH-DPAT), attenuates the increase in 5-HT produced by reuptake inhibitors, but not by fenfluramine. 3) The large increase in 5-HT produced by infusion of reuptake inhibitors into the hypothalamus is attenuated by their systemic administration. However, systemic injection of fenfluramine during its local infusion does not attenuate this increase. 4) Reuptake inhibitor pretreatment attenuates fenfluramine-induced increases in 5-HT. According to these criteria, the in vivo effects of the novel antiobesity drug sibutramine are consistent with its characterization as a 5-HT reuptake inhibitor and not a 5-HT releaser. Thus, sibutramine produced increases in hypothalamic 5-HT similar in magnitude to the effects of the known reuptake inhibitors, and the increase was attenuated by 8-OH-DPAT. Also, sibutramine attenuated fenfluramine-induced 5-HT release. Systemic administration of sibutramine failed to attenuate the increase in 5-HT produced by its local infusion, suggesting that this criterion is not applicable to compounds with low affinity for the 5-HT transporter.

L17 ANSWER 6 OF 6 MEDLINE on STN
AN 94282489 MEDLINE
DN PubMed ID: 7516805
TI The effects of BTS 54,505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the rat dorsolateral geniculate nucleus in vivo.
AU Scott G; Luscombe G P; Mason R
CS Department of Physiology and Pharmacology, University of Nottingham Medical School, Queens Medical Centre.
SO British journal of pharmacology, (1994 Jan) 111 (1) 97-102.
Journal code: 7502536. ISSN: 0007-1188.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199407
ED Entered STN: 19940810
Last Updated on STN: 19960129
Entered Medline: 19940725
AB 1. The effects of BTS 54,505, the primary amine metabolite of the non-tricylic putative antidepressant sibutramine, on the responses evoked by visual stimulation and ionophoretic application of noradrenaline (NA), 5-hydroxytryptamine (5-HT) and excitatory amino acids (EAAs) in the rat dorsolateral geniculate nucleus (dLGN) have been investigated. 2.

Ionophoretic application of 5-HT to dLGN neurones attenuated visually-evoked (n = 46), NMDA-evoked (n = 21) and AMPA-evoked responses (n = 21), while ionophoretic application of NA potentiated visually-evoked activity in these cells (n = 27). 3. Simultaneous application of BTS 54,505 with 5-HT (over 120 s) resulted in a prolongation of the recovery time (i.e. the period required by a neurone to recover by 50%, RT50) from the 5-HT-mediated suppression of discharge activity (approximately 275% increase in RT50). BTS 54,505 also prolonged the recovery time from a NA-mediated potentiation of firing (approximately 450% increase in RT50). These effects on recovery time are attributed to the inhibition of uptake of both 5-HT and NA by BTS 54,505. The amplitude of the response to 5-HT or NA was unaffected by co-ejection of BTS 54,505. 4. Ionophoretic application of N-methyl-D-aspartate (NMDA) produced a current-dependent increase in neuronal firing, as did application of the non-NMDA receptor agonist alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). A simultaneous 120 s application of BTS 54,505 inhibited the NMDA response in all cells studied (mean ED50 = 16 +/- 5 nA) but had no effect on AMPA-evoked activity in the majority of the same cells (n = 15/21).(ABSTRACT TRUNCATED AT 250 WORDS)

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